REMARKS

Claims 58-68 are pending. Claim 68 has been canceled. Claims 58, 59, 62, 63, and 67 have been amended to introduce certain format changes. Support for these amendments may be found at page 24, lines 4-5, of the specification. Applicants submit that these amendments raise no issue of new matter. Thus, claims 58-67 will be pending and under examination upon entry of the Preliminary Amendment.

Pursuant to the requirements of 37 C.F.R. §1.121, applicants annex hereto as **Exhibit A** a copy of the amended claims marked up to show the changes made herein relative to the previous version thereof.

In view of the arguments set forth below, applicants maintain that the Examiner's rejections made in the December 16, 2002 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 58-68 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Specifically, the Examiner alleged that the claims reciting the phrase "recognized by the B152 antibody" are vague and indefinite because it is unclear what is encompassed by "recognized."

In response to the rejection of claim 68, applicants point out that this claim has been canceled, rendering the rejection moot.

In response to the rejection of claims 58-67, applicants respectfully traverse and maintain that the term "recognized" as it pertains to antibody binding is well known in the art.

In support of their position, applicants point to page 1005 of Williams and Lemke, attached hereto as **Exhibit B**, to emphasize that the use of the term "recognize" to refer to an antibody's binding specificity is common in the art. Williams and Lemke state, in relevant part, that "[t]he variable regions of an immunoglobulin must be of a specific chemical structure with the ability to bind the antigen they 'recognize.'" In view of the art-recognized meaning of the term "recognize" with respect to antibody binding, applicants maintain that this term is definite.

The Examiner also rejected claim 58 as allegedly confusing in reciting "any complex formed between the first and second antibodies and the [EPMI-hCG] in the sample." In response, but without conceding the correctness of the Examiner's position, applicants note that claim 58, as amended, does not recite this phrase.

The Examiner also rejected claims 58 and 62 for failing to recite a positive limitation regarding antibody binding. In response, but without conceding the correctness of the Examiner's position, applicants note that the amended claims recite "which binds" instead of "capable of binding."

Finally, the Examiner rejected claim 59 as vague, indefinite, and lacking clear antecedent support in reciting "wherein one of the antibodies in each of steps a) and b) is bound to a solid support."

In response, but without conceding the correctness of the Examiner's position, applicants note that amended claim 59 does not recite the language objected to by the Examiner.

In view of the above remarks, applicants maintain that claims 58-67 satisfy the provisions of 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 58-67 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

Applicants understand the Examiner's rejection to be based upon the assertion that undue experimentation would be required because the specification does not provide a detailed description of the B152 epitope.

In response to the Examiner's rejection, applicants respectfully traverse. Throughout their response, applicants refer to the early pregnancy associated molecular isoform of hCG as "EPMI-hCG."

The Examiner's rejection fails to recognize that no structural knowledge of the epitope is required to practice the claimed methods and make and use the claimed kits. The antibodies used in these methods and kits can be made, in view of the specification, according to routine procedures of immunization, hybridoma production, and screening. None of these methods requires any structural knowledge of the epitope to which an antibody binds. For example, antibodies produced by immunization with intact hCG can be screened for affinity to hCG. A general method that can be employed in this regard is taught in Ehrlich at page 640, attached hereto as **Exhibit 9**. Notably, this method requires no structural knowledge of the epitope(s) involved in the antibody-antigen interactions.

Applicants also point to Ehrlich et al. (1985), attached hereto as **Exhibit 8**. At page 52, Ehrlich teaches three possible binding outcomes for the type of hCG assay described: (1) competitive inhibition, indicating that the two antibodies "[bind] in the same region on the hCG molecule," (2) no inhibition, indicating that the two antibodies bind "simultaneously to hCG without affecting the binding of each other," and (3) cooperativity, indicating that the two antibodies bind simultaneously and with a higher affinity for hCG than either antibody alone. Again, applicants note that no structural knowledge of epitopes is required to determine whether or not two antibodies bind to the same region on hCG.

It is clear from the teachings of Ehrlich that competitive binding assays using the working examples provided in the specification (e.g. at page 11, lines 26-33 through page 12, lines 1-21) can be used to identify antibodies with binding properties comparable to those of the working examples without undue experimentation.

In fact, the Examiner's allegation of undue experimentation is based upon the misguided assertion that it is necessary to synthesize glycosylated peptides that mimic the predicted epitope of EPMI-hCG. However, as applicants demonstrated above, neither such synthesis nor any other structural knowledge of epitopes is necessary to practice the claimed methods.

Finally, the Examiner's assertion that the specification lacks written description of EPMI-hCG is without merit. Applicants maintain that EPMI-hCG is not required to practice the claimed invention because antibodies that bind to EPMI-hCG can be generated using other immunogens that were known in the art. For example, as taught in the specification at page 31 lines 3-9, the immunogen used to elicit the B152 antibody itself was choriocarcinoma-derived hCG, designated "C5." The source, purification, and structure of the C5 immunogen are taught in Kardana et al. (1991), attached hereto as **Exhibit 11**, and in Elliot et al. (1997), attached hereto as **Exhibit 10**. The specification further teaches at page 31, lines 22-28, that JAR choriocarcinoma cells produce hCG recognized by the B152 antibody. Applicants maintain that either the C5 or JAR-derived hCG could be used to generate antibodies that bind to EPMI-hCG. In view of the teachings of the specification and the knowledge of choriocarcinoma-derived hCG in the prior art, applicants maintain that it is not necessary for the instant specification to further describe EPMI-hCG.

The Examiner also rejected claim 68 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had

possession of the claimed invention. Specifically, the Examiner alleges that the specification lacks support for isolated EPMI-hCG.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants point out that claim 68 has been canceled, rendering the objection moot.

In view of the above remarks, applicants maintain that claims 58-67 satisfy the provisions of 35 U.S.C. §112, first paragraph.

Obviousness-Type Double Patenting Rejection

The Examiner rejected claims 58-68 as allegedly unpatentable over claims 53, 59, 60, 65, 71, 72, and 77-82 of U.S. Serial No. 09/017,976, now U.S. Patent No. 6,500,627, issued December 31, 2002, under the judicially created doctrine of obviousness-type double patenting. The Examiner stated that although the claims are not identical, they are not patentably distinct from each other.

In response to the Examiner's rejection, but without conceding the correctness thereof, applicants will file a terminal disclaimer in the application at such time as the Examiner deems the pending claims to be otherwise in condition for allowance.

Marked-up version of amended claims

58. (amended): A method for predicting pregnancy outcome in a subject comprising the steps of:

(a) (i) contacting a first portion of a sample from the subject with a first antibody which binds to the ~~early pregnancy-associated molecular isoform of~~ EPMI-hCG that is recognized by the B152 antibody deposited with the American Type Culture Collection under Designation No. HB-12467;

(ii) contacting the sample resulting from (a)(i) with a second, labeled antibody ~~capable of binding~~which binds to ~~the early pregnancy-associated molecular isoform of~~ EPMI-hCG simultaneously with the first antibody;

(iii) measuring the amount of any ~~complex formed between the first and~~bound second ~~antibodies~~ antibody ~~and the early pregnancy-associated molecular isoform of hCG~~ in the sample, so as to thereby determine the amount of ~~the hCG isoform~~EPMI-hCG in the sample;

(b) (i) contacting a second portion of the sample from the subject with a third antibody which binds to intact non-nicked hCG;

(ii) contacting the sample resulting from (b)(i) with a fourth, labeled antibody ~~capable of binding~~which binds to intact non-nicked hCG simultaneously with the third antibody;

(iii) measuring the amount of ~~complex formed between the third and~~bound fourth ~~antibodies~~ antibody ~~and the intact hCG~~ in the sample, so as to thereby determine the amount of intact hCG in the sample, with the proviso that steps (a) and (b) can be performed in any order; and

(c) determining the ratio of the ~~early pregnancy-associated molecular isoform of hCG~~EPMI-hCG to intact hCG in the sample from the measurements performed in (a)(iii) and (b)(iii), wherein a ratio greater than 1 indicates a positive pregnancy outcome and a ratio less than 1 indicates a negative pregnancy outcome.

59. (amended): The method of claim 58, wherein ~~one of~~ each of the first and third antibodies ~~in each of steps (a) and (b)~~ is bound to a solid support.

62. (amended): A method for determining the amount of ~~early pregnancy-associated molecular isoform of~~ EPMI-hCG present in a sample comprising the steps of:

(i) contacting a sample from the subject with a first antibody which binds to the ~~early pregnancy-associated molecular isoform of~~ EPMI-hCG that is recognized by the B152 antibody deposited with the American Type Culture Collection under Designation No. HB-12467;

(ii) contacting the resulting sample with a second, labeled antibody ~~capable of binding~~which binds to ~~the early pregnancy-associated molecular isoform of~~ EPMI-hCG simultaneously with the first antibody; and

(iii) measuring the amount of ~~complex formed between the first and~~bound second ~~antibodies~~ antibody ~~and the early pregnancy-associated molecular isoform of hCG~~ in the sample, so as to thereby determine the amount of ~~the~~ EPMI-hCG ~~isoform~~ in the sample.

63. (amended): A diagnostic kit for predicting pregnancy outcome in a subject comprising:

(a) a first antibody, bound to a solid support, which binds to the ~~early pregnancy-associated molecular isoform of~~ EPMI-hCG that is recognized by the B152 antibody deposited with the American Type Culture Collection under Designation No. HB-12467;

(b) a second, labeled antibody which binds to ~~the early pregnancy-associated molecular~~

~~isoform of~~ EPMI-hCG simultaneously with the antibody of (a);

(c) a third antibody, bound to a solid support, which binds to intact non-nicked hCG;

(d) a fourth, labeled antibody which binds to intact non-nicked hCG simultaneously with the antibody of (c); and

(e) reagents permitting binding between the antibodies and their respective antigens in a sample from the subject.

67. (amended) An antibody which binds to the ~~early pregnancy-associated molecular isoform of~~ EPMI-hCG that is recognized by the B152 antibody deposited with the American Type Culture Collection under Designation No. HB-12467.

Foye's Principles of Medicinal Chemistry

Fifth Edition

David A. Williams, Ph.D.
Professor of Chemistry
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Thomas L. Lemke, Ph.D.
Associate Dean for Professional Programs and
Professor of Medicinal Chemistry
College of Pharmacy
University of Houston
Houston, Texas

LIPPINCOTT WILLIAMS & WILKINS
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Table 40.10. S me FDA-approv d MAb Therapeutic Ag nts

Generic Name	Trade Name	MAb Type	Description	Indication
Trastuzumab	Herceptin	Humanized	Binds to extracellular domain of human epidermal growth factor receptor (HER2) mediating an antibody-dependent cellular toxicity in cells that over express HER protein	Refractory breast cancer
Muromonab-CD3	Orthoclone-OKT3	Murine	First FDA-approved MAb therapeutic	Reversal of transplant rejection
Infliximab	Remicade	Chimeric	An anti-tumor necrosis factor-alpha MAb	Crohn's disease
Abciximab	ReoPro	Chimeric	LgG-derived F(ab')2 fragment blocks GPIIb/IIIa receptor site on activated platelet	Adjunct to PTCA for prevention of acute cardia complications
Ritiximab	Rituxan	Chimeric	Binds to the CD20 antigen found on >90% of all B-cell lymphomas	Treatment od B-cell non-Hodgkin's lymphoma
Basiliximab	Simulect	Chimeric	Binds to subunit of high-affinity IL-2 receptor found on activated T-cells	Prevention of transplant rejection
Daclizumab	Zenapax	Humanized	Binds to subunit of high-affinity IL-2 receptor found on activated T-cells	Prevention of transplant rejection
Palivizumab	Synagis	Humanized	Binds to "F" protein on surface of virus preventing virus from infecting cells	Respiratory syncitial virus prophylaxis
Gemtuzumab Ozoganicin	Mylotarg	Fusion MAb	Composed of humanized anti-CD33 MAb conjugated with the cytotoxic antibiotic calicheamicin	Treatment of CD33 positive acute myeloid leukemia

munogenic murine MAbs were useless in chronic therapy. Thus, some approach was needed to eliminate the unwanted immune response (HAMA) in patients.

The variable regions of an immunoglobulin must be of a specific chemical structure with the ability to bind to the antigen they "recognize." The part within the variable region that forms the intermolecular interactions with the antigen is the complementarity determining region (CDR). The variable domains of antibody light and heavy chains each contain three CDRs.

It was determined that immune responses against the mouse-produced MAbs were directed against both the variable and the constant regions of the antibody. Human and murine antibodies are very homologous in chemical structure. Thus, a MAb should be engineered to decrease the immunogenicity of a MAb by replacing the mouse constant regions of an IgG with human constant regions, making the antibody less mouse-like (185, 195–199). In practice what generally occurs is the variable heavy and variable light chain domains (CDRs) of human immunoglobulins are replaced with those of a murine antibody which possesses the requisite antigen specificity. This "chimeric" MAb will retain its ability to recognize the antigen (a property of the murine MAb), retain the many effector functions of an immunoglobulin (both murine and human), while being much less immunogenic (a property of a human immunoglobulin). A chimeric MAb, containing approximately 70% human sequence, will have a longer half-life than its murine counterpart in a human patient. Therapeutic monoclonal antibodies that are chimeric include abciximab, ritiximab, infliximab, and basiliximab.

While the discovery that the conserved structure of antibodies, in particular IgGs, across many species suggested the possibility of chimeric antibodies, the realization that the homology extended to the antigen-binding site facilitated the engineering of humanized immunoglobulins. Advances in phage display technology and the production of transgenic animals has lead to the production of humanized or fully human MAbs (185, 195–199). Functional human antibody fragments (e.g., Fab fragments) can be displayed on the surface of bacteriophages. A bacteriophage, also called a phage, is a virus that infects bacteria. The expression of these human antibody fragments on the phage surface has facilitated efficient screening of large numbers of phage clones (phage display) for antigen-binding specificity (200). Once a fragmented with the requisite antigen specificity is selected, it can be isolated and engineered into a humanized MAb (replacing up to 95% of the murine protein sequence) or a fully human MAb (100% human sequence). Transgenic strains of mice have been genetically engineered to possess most and now all of the essential human antibody genes. Thus, upon immunization with a foreign antigen, the transgenic mice will develop humanized or fully human antibodies in response. Both of these techniques, while very complex and expensive, have yielded FDA-approved humanized antibody pharmaceuticals such as daclizumab, palivuzumab, and trastuzumab. The half-life of humanized antibodies are dramatically enhanced (from hours to weeks) and immunogenicity is drastically reduced.

Monoclonal Antibody Therapeutic Agents

Hybridoma technology and advanced antibody engineering has led to the design of an increasing number of site-directed therapeutic agents for the treatment and prevention of transplant rejection, therapy in rheumatoid